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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,110	07/03/2006	Robert Peter Millar	20747/300	4173

7590 06/12/2007

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,110	MILLAR, ROBERT PETER	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33,35,37,39-41,43 and 45-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15-26,29-33,35,37,39-41,43 and 45-60* is/are rejected.

7)☒ Claim(s) *13,14,27 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/4/05, 8/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Upon further consideration, the requirement for election and restriction mailed 12/13/2006 is vacated. The inventions are related but distinct as described in the previous office action but there is not a significant burden to search all of Groups I-IV. An examination on the merits of claims 1-33, 35, 37, 39-41, 43 and 45-60 appears below.

Claim Objections

2. Claim 9 is objected to because of the following informalities: Na-Glu should be Nal-Glu as spelled in citation number 80 on the Information Disclosure Statement filed 8/28/2006.

3. Claim 11 is objected to because of the following informalities: triptorelin appears twice in the Markush group. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12, 15-26, 29-33, 35, 37, 39-41, 43 and 45-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure,

physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

6. Claims 1-12, 15-26, 29-33, 35, 37, 39-41, 43 and 45-60 are drawn to GnRH analogues conjugated to hormone moieties and their derivatives. The specification discloses the complete structure of GnRH analogues conjugated to a variety of steroid hormones. The claimed genus is much broader than this well-defined subgenus because the limitation hormone includes a large number of compounds that fall in entirely separate structural and functional classes.

7. A hormone is a chemical messenger from one cell (or group of cells) to another. All multicellular organisms produce hormones including plants. The function of hormones is to serve as a signal to the target cells, and the action of hormones is determined by the pattern of secretion and the signal transduction of the receiving tissue. The best-known animal hormones are those produced by endocrine glands of vertebrate animals, but hormones are produced by nearly every organ system and tissue type in a multicellular organism. The three major classes of hormones in humans include amine-derived hormones, peptides, and lipid-derived hormones.

8. Amine-derived hormones are derivatives of the amino acids tyrosine and tryptophan. Examples are melatonin, serotonin, triiodothyronine, epinephrine, norepinephrine, dopamine, corticotrophin-releasing hormone, catecholamines and thyroxine.

9. Peptide hormones consist of chains of amino acids ranging from less than 10 to over 100 amino acids in length. Each peptide hormone has a unique amino acid sequence that dictates its structure and function. Examples of peptide hormones include antimullerian hormone, adiponectin, adrenocorticotropic hormone, angiotensin, antidiuretic hormone, atrial-natriuretic, calcitronin, cholecystokinin, corticotropin-releasing hormone, erythropoietin, follicle-stimulating

hormone, gastrin, ghrelin, glucagons, gonadotropin-releasing hormone, growth hormone-releasing hormone, human chorionic gonadotropin, human placental lactogen, growth hormone, inhibin, insulin, insulin-like growth factor, leptin, luteinizing hormone, melanocyte stimulating hormone, oxytocin, parathyroid hormone, prolactin, relaxin, secretin, somatostatin, thrombopoietin, thyroid-stimulating hormone, and thyrotropin-releasing hormone. More complex protein hormones bear carbohydrate side chains and include luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone.

10. Lipid-derived hormones are derivatives of lipids such as linoleic acid and arachidonic acid as well as phospholipids. The main classes of lipid-based hormones are the steroid hormones that are derived from cholesterol and the eicosanoids. Examples of steroid hormones are cortisol, aldosterone, testosterone, dehydroepiandrosterone, androstenedione, dihydrotestosterone, estradiol, estrone, estriol, progesterone, calcitriol, and prostaglandins. Examples of eicosanoids are leukotrienes, prostacyclin and thromboxane.

11. Despite this breath, the specification only provides evidence that applicant was in possession of GNRH conjugated to steroid hormones at the time the invention was filed (see Figures 1A and 1B for example). Although other hormones are described in the prior art, their use in conjugation to GNRH is not known. The specification fails to describe in any detail how hormones other than steroid hormones can be conjugated to GNRH analogues while retaining the hormonal activity of GNRH and the plasma protein binding activity of the partner hormone. Given the diversity in sequence, size and tertiary structure of the peptide hormones, this is a complex problem. Despite this complexity, the specification fails to address for example how the GNRH analogue can be attached to the peptide hormone without disrupting the intended

activities and functional characteristics. Furthermore, the specification fails to describe the use of peptide or amine hormones to prolong the half-life of GNRH in the bloodstream. Finally, the specification does not describe the plasma hormone binding proteins specific to hormones other than steroid hormones.

12. As broad as the genus hormone is, the genus hormone derivatives is even broader. The specification defines derivative of a hormone as a structure modified from the structure of the hormone found in nature that may or may not retain its hormonal activity but does retain its ability to bind to plasma hormone binding protein. The plasma hormone binding proteins described in the specification are globulins such as cortisol binding globulin, sex hormone binding globulin, progesterone binding globulin and serum albumin. Steroid hormone derivatives that retain their ability to bind to these proteins are well-defined in the specification and include those which have been modified by adding a hydroxyl group at position 11, 17 or 21 such as 11-α-hydroxyprogesterones and 21-hydroxyprogesterones. The general relationship between structure and the function of binding to plasma hormone binding protein is also provided in the specification. For example, the specification states that in order to interact with sex hormone binding globulin, a steroid must contain a 17-β-hydroxyl group and that other features, such as the addition of a hydroxyl or a keto group at C11 and modification of carbon 2, 6, 9 and 11 in the steroid nucleus have negative effects on binding affinity. In contrast, the specification fails to describe the structure, partial structure or guidance on the structure/function relationship for derivatives of hormones other than steroid hormones or even examples of plasma hormone binding protein specific to the amine-derived and peptide hormones.

13. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). With the exception of GNRH conjugated to steroid hormones and their derivatives, the skilled artisan cannot envision the detailed chemical structure of the GNRH conjugates. Therefore, only GNRH analogues conjugated to steroid hormones and their derivatives, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

14. Claim 9 is further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the structure of D21775 is not described in the specification or known in the prior art.

15. Claims 45-51 and 56-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modifying GNRH analogues to increase their half-life by conjugating them to steroid hormones, does not reasonably provide enablement for conjugating GNRH analogues to all other types of hormones. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The factors to be considered in

predictability associated with increasing the half-life of GNRH analogues by conjugating them to steroid hormones. In contrast, many peptide hormones are known to exhibit short half-lives *in vivo*, a barrier to their use in pharmaceutical applications. See for example Doyle & Egan, *Recent Prog Horm Res.*, **2001**, *56*, 377-99 for a discussion of glucagons-like peptide-1 and Evers *et al.*, *Ann Surg.*, **1991**, *213*, 190-8 for a discussion of somatostatin. Given that many peptide hormones have short half-lives, it is unlikely that that conjugating them to GNRH will increase the half-life of the GNRH.

The Relative Skill of Those in the Art

18. The relative skill of those in the art is high.

The breadth of the claims

19. The claims are exceptionally broad. The limitation hormone includes a large number of compounds such as: the amine derived hormones melatonin, serotonin, triiodothyronine, epinephrine, norepinephrine, dopamine, corticotrophin-releasing hormone, catecholamines and thyroxine; the peptide hormones antimullerian hormone, adiponectin, adrenocorticotropic hormone, angiotensin, antidiuretic hormone, atrial-natriuretic, calcitronin, cholecystokinin, corticotropin-releasing hormone, erythropoietin, follicle-stimulating hormone, gastrin, ghrelin, glucagons, gonadotropin-releasing hormone, growth hormone-releasing hormone, human chorionic gonadotropin, human placental lactogen, growth hormone, inhibin, insulin, insulin-like growth factor, leptin, luteinizing hormone, melanocyte stimulating hormone, oxytocin, parathyroid hormone, prolactin, relaxin, secretin, somatostatin, thrombopoietin, thyroid-stimulating hormone, thyrotropin-releasing hormone, luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone; and the lipid-derived hormones cortisol, aldosterone,

determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and are as follows:

The Nature of the Invention

16. Claims 45-51 and 56-60 are drawn to a method for modifying GNRH analogues to increase their half-life by conjugating them to hormone moieties capable of binding to a plasma hormone binding protein.

The State of the Prior Art and its Predictability or Unpredictability

17. The GNRH-hormone conjugates are not known in the prior art. However, as stated in the specification, the prior art is replete with information on the binding of steroid hormones to plasma hormone binding proteins such as cortisol binding globulin, sex hormone binding globulin, progesterone binding globulin and serum albumin (see Mickelson *et al.*, Siiteri *et al.*, and Westphal *et al.*, cited references 94, 107 and 110, respectively, on the Information Disclosure Statement filed 8/28/200694). For example, steroid hormones may be modified by adding a hydroxyl group at position 11, 17 or 21 such as in the case of 11-α-hydroxyprogesterones and 21-hydroxyprogesterones. In addition, it is known in the prior art cited in the specification that a steroid must contain a 17-β-hydroxyl group to preserve binding (Burton & Westphal and Cunningham *et al.*, cited references 76 and 78 respectively, on the Information Disclosure Statement filed 8/28/2006). Other changes, such as the addition of a hydroxyl or a keto group at carbon 11, and modification of carbons 2, 6, 9 and 11 in the steroid nucleus have negative effects on binding affinity (Cunningham *et al.*). Given this level of structural information on the steroid-plasma hormone binding interaction, there is a high level of

testosterone, dehydroepiandrosterone, androstenedione, dihydrotestosterone, estradiol, estrone, estriol, progesterone, calcitriol, prostaglandins, leukotrienes, prostacyclin and thromboxane.

The Amount of Direction or Guidance Presented and the Presence of Working Examples

20. The specification provides specific examples and ample guidance on the conjugation of GNRH analogues to steroid hormones but no examples or guidance for conjugating GNRH analogues to all other hormones. In the absence of such guidance, the skilled artisan would not know how to attach the GNRH analogue to the peptide or lipid-based hormone without disrupting the hormone's interaction with blood plasma proteins. Furthermore, the specification fails to provide guidance on the use of peptide hormones to increase the half-life of compounds such as GNRH analogues. In the absence of such guidance, the skilled artisan would not know how to use peptide hormones, compounds which generally possess low half-lives, to increase the half-life of GNRH analogues. The prior art which reports on the low half-life of peptide hormones, teaches against the use of such compounds to increase the half-life of other molecules such as GNRH. Therefore, it is essential that the specification provide detailed instruction and examples to guide the skilled artisan toward this unorthodox use of peptide hormones.

The Quantity of Experimentation Necessary

21. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining how conjugation to a peptide or lipid-derived hormone can be used to increase the half-life of GNRH analogues. The design of long-lasting derivatives of peptide and lipid-based hormones would require years of inventive effort. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Allowable Subject Matter

22. Claims 13, 14, 27 and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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cmb

6/11/07
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PRIMARY EXAMINER